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CONTINUING DATA AS CLAIMED BY APPLICANT-
THIS APPLN IS A CIP OF 08/019,864 02/19/93
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* SMALL ENTITY *

TITLE
TECHNETIUM-99M LABELED PEPTIDES FOR IMAGING INFLAMMATION

PRELIMINARY CLASS: 514

(se r vers)

APPLICATION FOR UNITED STATES LETTERS PATENT IN THE UNITED STATES PATENT AND TRADEMARK OFFICE (Case No. 90,1104-D)

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TECHNETIUM-99m LABELED PEPTIDES FOR IMAGING INFLAMMATION

This is a continuation-in-part of U.S. Patent Application Serial No. 08/019,864, filed February 19, 1993, which is a continuation-in-part of U.S. Patent Application Serial No. 07/653,012, filed on February 8, 1991.

BACKGROUND OF THE INVENTION

1. Field of the Invention

This invention relates to compositions that are radiolabeled scintigraphic imaging agents, methods of using these compositions and methods for producing such radiolabeled compositions. Specifically, the invention relates to technetium-99m labeled scintigraphic imaging agents that are compositions of a polysulfated glycan or mixture thereof and a compound comprising a polybasic moiety covalently linked to a radiolabel binding moiety radiolabeled with technetium-99m (Tc-99m). Methods and kits for making such compositions, and methods for using such compositions to image sites of infection and inflammation in a mammalian body are also provided.

2. Description of the Prior Art

There is a clinical need to be able to determine the location and/or extent of sites of focal or localized infection and inflammation. In a substantial number of cases conventional methods of diagnosis (such as physical examination, x-ray, CT and ultrasonography) fail to identify such sites (*e.g.*, an abscess). Although biopsy may be resorted to, it is preferable to avoid such invasive procedures, at least until they are diagnostically appropriate to identify the pathogen responsible for an abscess at a known location. Identifying the site of such "occult"' infection is important because rapid localization and identification of the problem is critical to effective therapeutic intervention.

In the field of nuclear medicine, certain pathological conditions can be localized or the extent of such conditions determined by imaging the internal distribution of administered radioactively-labeled tracer compounds (i.e. radiotracers or radiopharmaceuticals) that

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The preferred protecting group has the formula -CH_2-NHCOR wherein R is a lower alkyl having 1 and 8 carbon atoms, phenyl or phenyl-substituted with lower alkyl, hydroxyl, lower alkoxy, carboxy, or lower alkoxycarbonyl.

Labeling with Tc-99m is an advantage of the present invention because the nuclear and radioactive properties of this isotope make it an ideal component of a scintigraphic imaging agent. This isotope has a single photon energy of 140 keV and a radioactive half-life of about 6 hours, and is readily available from a ^{99}Mo-^{99m}Tc generator. Other radionuclides known in the prior art have effective half-lives which are much longer (*for example*, ^{111}In, which has a half-life of 67.4 h) or are toxic (*for example*, ^{125}I).

Each polybasic peptide-containing embodiment of the invention is comprised of a sequence of amino acids. The term amino acid as used in this invention is intended to include all L- and D- amino acids, naturally occurring and otherwise. Reagents comprising polybasic peptides provided by the invention include but are not limited to the following (the amino acids in the following peptides are L-amino acids except where otherwise indicated):

acetyl-KC_{Acm}GC_{Acm}QAPLYKKIIKKLLES
acetyl-KKC_{Acm}GC_{Acm}QAPLYKKIIKKLLES
acetyl-KKKC_{Acm}GC_{Acm}QAPLYKKIIKKLLES
acetyl-KKKKC_{Acm}GC_{Acm}QAPLYKKIIKKLLES
acetyl-KKKKKC_{Acm}GC_{Acm}QAPLYKKIIKKLLES
acetyl-KC_{Acm}GC_{Acm}GGPLYKKIIKKLLES
acetyl-KKC_{Acm}GC_{Acm}GGPLYKKIIKKLLES
acetyl-KKKC_{Acm}GC_{Acm}GGPLYKKIIKKLLES
acetyl-KKKKC_{Acm}GC_{Acm}GGPLYKKIIKKLLES
acetyl-KKKKKC_{Acm}GC_{Acm}GGPLYKKIIKKLLES

Polybasic peptide embodiments of the present invention may be chemically synthesized *in vitro*. Peptides of the present invention can generally advantageously be prepared on a peptide synthesizer. The peptides of this invention can be synthesized wherein the radiolabel binding moiety is covalently linked to the peptide during chemical *in vitro* synthesis, using techniques well known to those with skill in the art. Such peptides covalently-linked to the radiolabel binding moiety upon synthesis are advantageous because specific sites of covalent linkage can be determined therein.

Radiolabel binding moieties of the invention may be introduced into the target specific

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polybasic compound is a peptide and the peptide is synthesized by solid phase peptide synthesis.

18. The reagent of Claim 2 wherein the radiolabel binding moiety is covalently linked to the peptide during *in vitro* chemical synthesis.

19. The reagent of Claim 18 wherein the radiolabel binding moiety is covalently linked to the peptide during solid phase peptide synthesis.

20. A composition of matter having the formula:

acetyl-KC$_{Acm}$GC$_{Acm}$QAPLYKKIIKKLLES
acetyl-KKC$_{Acm}$GC$_{Acm}$QAPLYKKIIKKLLES
acetyl-KKKC$_{Acm}$GC$_{Acm}$QAPLYKKIIKKLLES
acetyl-KKKKC$_{Acm}$GC$_{Acm}$QAPLYKKIIKKLLES
acetyl-KKKKKC$_{Acm}$GC$_{Acm}$QAPLYKKIIKKLLES
acetyl-KC$_{Acm}$GC$_{Acm}$GGPLYKKIIKKLLES
acetyl-KKC$_{Acm}$GC$_{Acm}$GGPLYKKIIKKLLES
acetyl-KKKC$_{Acm}$GC$_{Acm}$GGPLYKKIIKKLLES
acetyl-KKKKC$_{Acm}$GC$_{Acm}$GGPLYKKIIKKLLES
acetyl-KKKKKC$_{Acm}$GC$_{Acm}$GGPLYKKIIKKLLES.

21. The composition of matter of Claim 20 that is labeled with technetium-99m.

22. A composition of matter comprising a composition comprising the reagent of Claim 20 and polysulfated glycan.

23. The composition of Claim 22 that is labeled with technetium-99m.

24. A method for imaging a site of inflammation within a mammalian body comprising mixing whole blood with an amount from about 1 microgram to 100 milligrams of a polysulfated glycan to form a mixture, and further adding to the mixture an amount from about 1 microgram to 100 milligrams of a composition of matter comprising a technetium-99m radiolabeled reagent according to Claim 1 to form a radiolabeled mixture, administering said radiolabeled mixture to an animal having a site of inflammation *in vivo*, and detecting a radioactive signal from the Tc-99m localized at the site of inflammation.

25. A composition of matter comprising a reagent according to Claim 24.

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